Symposium

Choroidal metastases: Origin, features, and therapy

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The choroid is the most common ocular site for metastatic disease, owing to abundant vascular supply. The primary cancers that most commonly lead to choroidal metastases include breast cancer (40-47%) and lung cancer (21-29%). Bilateral, multifocal metastases are most often secondary to breast cancer, whereas unilateral, unifocal metastasis are more commonly found with lung cancer. The treatment of choroidal metastasis depends on the systemic status of the patient and number, location, and laterality of the choroidal tumors. Treatment options include observation in patients with poor systemic status or those with resolved or asymptomatic disease; systemic chemotherapy, immunotherapy, hormone therapy, or whole eye radiotherapy if the metastases are active, multifocal and bilateral; plaque radiotherapy, transpupillary radiotherapy, or photodynamic therapy for active, solitary metastasis; and enucleation for those with blind painful eye. A database search was performed on PubMed, using the terms "choroidal metastasis," or "choroidal metastases," in combination with terms such as "treatment," "features," or "diagnosis." Relevant articles were extracted and reviewed.

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The first documented case of choroidal metastasis was by Perls in 1872.[1] Although once considered a rare entity, choroidal metastases are now considered the most common intraocular malignancy in the adult population. In a review of patients dying from the malignancy, 8% displayed choroidal metastases on autopsy.[2] Choroidal metastases tend to become apparent late in the course of malignancy, and are associated with disseminated disease and poor prognosis.[1-5]

The choroid is the most common ophthalmic site for metastatic disease, and it is postulated that hematogenous dissemination of metastasis from remote major sites typically leads to the high flow choroidal vasculature with metastatic disease.[4-8] The choroid provides a vascular avenue for tumor emboli to sequester and allows an environment receptive to growth.[7] In this article, we will review the common primary tumor origins, the salient features of metastases, and treatment options available for these lesions.

A database search was performed on PubMed, using the terms "choroidal metastasis," or "choroidal metastases," in combination with terms such as "treatment," "features," or "diagnosis." Relevant English language articles were extracted, with reference lists of the articles reviewed for applicable articles. In cases of non-English language articles, if the abstract was translated into English, the article was referenced as (abstract) in the citation.

Ophthalmic Features and Origin

The choroid is the most common ocular structure affected by metastases.[5] In a review of 520 patients presenting with 950 metastases to the uvea, the choroid was involved in 88% of cases.[5] Other studies have similarly shown metastases to the choroid in 57-73% of cases.[3,4] Given the predominance of metastases involving the postequatorial region and their frequent development of subretinal fluid, patients typically present with blurred vision (70-81%).[5,9] The other less common manifestations include flashes and floaters (5-12%), and pain (5-14%).[5,10,11] However, 9–11% of patients present with no symptoms and lesions may be found on routine ocular examination [Fig. 1].[5,9]

Based on a review of 479 eyes with choroidal metastasis by Shields *et al*., choroidal metastases generally appear as a yellow subretinal mass (94%) associated with subretinal fluid (73%).[5] Infrequently, the mass can appear with an orange color, typically with renal cell carcinoma, carcinoid tumor, or thyroid cancer metastases (3%) or brown-gray, usually with metastatic melanoma (3%). The majority of eyes (72%) had one focus, with mean number of tumors per eye being 1.6 (median: 1, range: 1-13).[5] In general, the lesions were located posterior to the equator in 88% of cases. Choroidal metastases were lateral (35%), superior (22%), inferior (17%), nasal (14%) and macular (12%). Measurement of the largest metastases revealed an average base of 9 mm and a thickness of 3 mm.[5] Bilateral, multifocal metastases were most common secondary to breast cancer, while unilateral, unifocal metastasis were more common with lung cancer.[5,12]

Breast carcinoma is the most common primary source of choroidal metastasis providing origin in 40-53% of cases, with 92% of patients having concurrent systemic metastases [Table 1].[4,5,12-15] In a study of 349 eyes with choroidal metastasis from breast carcinoma by Demirci *et al*., the tumors were postequatorial in 89% cases and multifocal in 48% cases.[12] Mean survival time from diagnosis of ocular metastases was 21 months.[12]

Lung cancer is the second most common source of choroidal metastasis accounting for 20-29% of cases.[4,5] Shah *et al*.

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Table 1: Choroidal metastases: Origin, features and therapy. Primary tumor origins

Primary tumor location (*n*=479)	Number (%)
Breast	252 (53)
Lung	98 (20)
Gastrointestinal	18 (4)
Kidney	8 (2)
Prostate	10 (2)
Skin	5 (1)
Other	17 (4)
Unknown	71 (15)

Adapted from a clinic-based study[5]

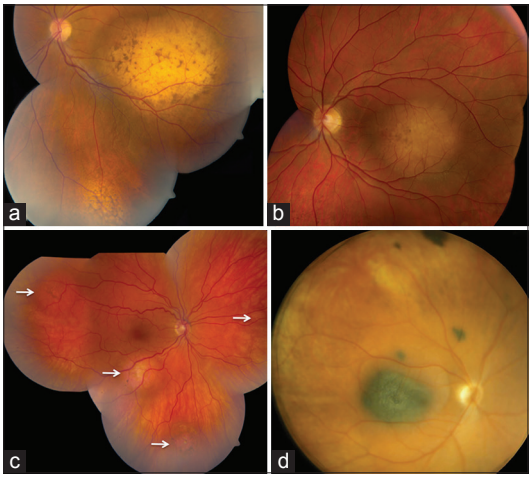

Figure 1: Choroidal metastases. (a) Multifocal amelanotic metastases with overlying brown lipofuscin deposits from breast carcinoma. (b) Unifocal amelanotic metastasis with overlying brown lipofuscin deposits and subretinal fluid from lung carcinoma. (c) Multifocal orange-colored metastases (arrows) with overlying brown lipofuscin deposits from lung carcinoid tumor. (d) Multifocal pigmented metastases from skin malignant melanoma

analyzed the relationship of uveal metastases from lung cancer in 194 patients with 374 tumors and found that choroidal metastases from lung cancer tend to be unifocal (77%) and unilateral (82%).[16] Mean survival time following diagnosis of ocular metastases was 12 months.[16]

Less common primary tumors causing choroidal metastases include carcinoma of the gastrointestinal tract (4%), prostate (2%), kidney (2-4%), and skin (2%).[4,5,10] Rare primary carcinomas are metastasizing to choroid include tumors arising from the submandibular gland, thyroid, contralateral choroid, testes, ovaries, urothelial tract, neuroendocrine tumor, and sarcoma.[5,7-9,10,17-22] Most patients with choroidal metastasis have known systemic cancer at the time of eye diagnosis, but in 34% of cases, the choroidal metastasis precedes diagnosis of systemic cancer. Of those without known cancer, the primary tumor sites included lung cancer (7%), breast cancer (35%), and about 50% of patients with the primary site not found.[5]

Diagnosis

The differential diagnosis of choroidal metastases includes choroidal melanoma, hemangioma, granuloma, osteoma, and sclerochoroidal calcification. In cases without a history of a primary malignancy, diagnosis can be difficult, especially with roughly one-half of cases with no detectable primary tumor.[5] Distinct features on ophthalmoscopy and various imaging modalities distinguish choroidal metastases from other choroidal tumors.

Autofluorescence

Autofluorescence (AF) is a noninvasive imaging technique, which allows assessment of intrinsic AF of ocular tissues. The most common source is lipofuscin, a compound composed of digested outer photoreceptors stored in the retinal pigment epithelium.[23] On ophthalmoscopic examination, choroidal metastases often have overlying subretinal fluid and lipofuscin that typically appear as scattered clumps of brown pigment.[23-26] AF shows hypoautofluorescence of the tumor with overlying areas of bright 3+ hyperautofluorescence correlating to the deposits of lipofuscin and 2+ hyperautofluorescence of subretinal fluid.[26] These findings not only define tumor surface characteristics, but can also delineate progressing tumor margins.[23-26]

Ultrasonography

Ultrasonography determines tumor dimensions and echogenicity and allows differentiation of metastases from other intraocular neoplasms, particularly melanomas. In contrast to choroidal melanomas which display medium to low reflectivity on A-scan and are acoustically hollow on B-scan, choroidal metastases have a higher reflectivity on A-scan and appear echo-dense on B-scan, with a significantly lower height to base ratio compared to melanomas.[3,5,27,28] Rarely, cavitary variant has been described with carcinoid metastases, a feature previously only associated with choroidal melanoma.[29] <0.5% of metastases present with a "mushroom" or "collar-button" configuration.[5,30] Thickness tends to correlate to origin of metastases, with a mean thickness of metastases secondary to melanoma measuring 1 mm, breast 2 mm, lung and prostate 3 mm, and gastrointestinal and kidney measuring 4 mm.[5]

Optical Coherence Tomography

Initial studies by Arevalo *et al*. utilizing spectral domain optical coherence tomography (OCT) characterized the surface overlying choroidal metastasis as undulating, with thickening of the retinal pigment epithelium along with overlying subretinal fluid (86%).[31] Iuliano *et al*. described similar findings in a case of bilateral choroidal metastases, along with areas of hyperintense irregularities in the photoreceptor layer.[32] Al-Dahmash *et al*. later used enhanced depth imaging OCT (EDI-OCT) on 14 eyes with choroidal metastases to assess the deeper retinal and choroidal morphology, and found a characteristic "lumpy bumpy" choroidal surface in 9 (63%), with compression of the overlying choriocapillaris in 93% of cases, and irregularities of the outer retinal layer in 11 cases (79%).[33] EDI-OCT also allows detection of micro-metastases often in apparent with fundoscopy.[33]

Fluorescein Angiography

Fluorescein angiography (FA) can provide ancillary data necessary to differentiate choroidal metastases from choroidal melanomas. FA typically displays a hypofluorescent pattern in early arterial phases, with hyperfluoresence in the late

venous phases, later than most choroidal melanomas.[3,25,26] Choroidal metastases also contain dilated retinal capillaries with a pinpoint leakage at the tumor border in 73% of cases as compared to melanoma in 16% of cases.[34]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) often shows a well-demarcated choroidal mass that appears isointense on T1-weighted images and hypointense on T2-weighted images.[29,35] However, De Potter *et al*. have documented an unusual presentation of a metastasis on MRI, describing the lesion as a thin, diffuse choroidal mass, more consistent with a choroidal melanoma with optic nerve involvement. The lesion was hyperintense on T1 and hypointense on T2. After enucleation, pathology revealed the mass to be a mucin-secreting adenocarcinoma.[36]

Fine Needle Aspiration Biopsy

In cases of unidentified primary source and indeterminate diagnostic findings, fine needle aspiration biopsy can provide cytological evidence of metastasis versus primary occurrence.[3,37]

For posterior segment lesions with no retinal detachment, biopsy is obtained through a pars plana and transvitreal approach while cases of overlying retinal detachment necessitate a trans-scleral equatorial approach.[37]

Treatment

The treatment of choroidal metastasis depends on the systemic status, number of choroidal tumors, location, and laterality. Observation is preferred in patients with poor systemic status; systemic chemotherapy, immunotherapy, hormone therapy, or whole eye radiotherapy if the metastases are multifocal and bilateral; plaque radiotherapy, transpupillary radiotherapy, or photodynamic therapy (PDT) for solitary metastasis; and enucleation for blind painful eyes.

Systemic Treatment

Systemic chemotherapy, immunotherapy or hormone therapy is the preferred treatment strategy in patients with bilateral, multifocal choroidal metastases. The choice of drug depends on the type of primary cancer. Fenestrated endothelium in the choriocapillaris allows entry of medications into the choroidal tumors to provide effective tumor control.[5]

A large proportion of choroidal metastases from breast carcinomas express estrogen or progesterone receptors, making therapy with tamoxifen and aromatase inhibitors effective.[38,39] Manquez *et al*. showed tumor regression in 10 out of 17 patients with hormone receptor-positive breast cancer treated with aromatase therapy over a mean follow-up period of 20 months.[39] Regression of choroidal metastasis from breast and lung carcinoma after systemic chemotherapy has been noted.[40-43] In a study of 4 patients with choroidal metastasis treated with systemic chemotherapy alone, tumor regression occurred in 3 patients.[44]

External Beam Radiotherapy

External beam radiotherapy (EBRT) at a dosage of 40-60 Gy causes tumor regression in 85-93% of patients with vision improvement or stabilization in 56% of eyes.[19,45-48] However, the extended treatment period of EBRT makes the treatment inconvenient and impractical in critically ill-patients with poor life prognosis. Radiation related complications include cataract (7%), radiation retinopathy (3%), exposure keratopathy (3%), optic neuropathy (2%), and neovascularization of iris (2%).[48]

Gamme Knife Radiosurgery

Gamma knife radiosurgery (GKR) has been used in the treatment of uveal melanomas as well as choroidal metastases.[3] In this technique, multiple gamma rays are focused on the lesion, and usually requires an average dosage of 30 Gy administered over 10 days. Two reports have documented the success of GKR with choroidal metastases, with the larger study comprised of 57 eyes, documenting 100% control in Grade 1 lesions and 63% response in all choroidal metastases overall, over a mean follow-up period of 7 months.[45,46]

Proton Beam Radiotherapy

Proton beam radiotherapy (PBT) allows for more focused irradiation, as compared to GKR, as protons are delivered through beam and travel through tissue depth based on the amount of energy they contain, with less scatter to nearby tissues.[48] Tsina *et al*. showed regression of choroidal metastases in 84%, and stability of lesion in 14% of eyes treated with PBT over a mean follow-up period of 5 months, with 47% of patients maintaining or improving visual acuity. The average dosage administered was 28 Gy delivered over two treatments.[49] Complications included madarosis (28%), lid burns (17%), iris neovascularization and neovascular glaucoma (8%), cataract (11%), radiation maculopathy (19%) and radiation papillopathy (22%).[49,50]

Plaque Radiotherapy

Plaque radiotherapy provides more focused, targeted radiotherapy than EBRT resulting in good tumor control and fewer ocular complications. Shields *et al*. treated 36 patients with choroidal metastases with plaque radiotherapy and observed immediate regression in 100% of patients, with lasting regression in 94% over a mean follow-up period of 11 months.[51] Stable or improved vision was achieved in 58%. The average dosage was 69 Gy to the tumor apex, usually, applied over 3 days. Radiation retinopathy and/or papillopathy occurred in three patients (8%).[51] Lim and Petrovich documented tumor shrinkage and subretinal fluid resolution in all 5 eyes treated with plaque radiotherapy, with stable or improved vision in 60% over a mean follow-up period of 10 months. Late radiation complications included optic nerve atrophy (40%) and radiation retinopathy (20%).[51,52]

Transpupillary Thermotherapy

Transpupillary thermotherapy (TTT) uses diode laser to administer heat to the choroid and retinal pigment epithelium, inducing tumor necrosis.[4] The technique was first used as an adjuvant therapy for choroidal melanoma incompletely responsive to plaque radiotherapy.[53] Expansion of the technique into other intraocular tumors has led to the treatment of choroidal metastases.[54-56] In a study of 59 eyes with choroidal metastasis managed with TTT as the primary treatment, 71%

of eyes showed regression or inhibition of growth, while 7% showed progression over a follow-up period of 15 months.[54]

Photodynamic Therapy

Photodynamic therapy causes tumor necrosis through the production of reactive singlet oxygen, as well intravascular thrombosis and subsequent tumor infarction through verteporfin. PDT has been used in the management of several ocular conditions, including age-related macular degeneration, retinal astrocytic hamartoma, choroidal hemangiomas, and melanomas.[3] PDT has been successfully used as either primary or secondary treatment of choroidal metastases.[57-62] Kaliki *et al*. documented tumor regression in 7 of 9 patients, with stable or improved vision in all but one case over an average follow-up period of 17 months.[62]

Intravitreal Antivascular Endothelial Growth Factor Injection

Intravitreal antivascular endothelial growth factor (VEGF) injections have redirected the management of neovascular ocular conditions. With the dependence of metastases on neovascularization for growth, the use of intravitreal bevacizumab and ranibizumab to prevent angiogenesis is an effective modality of treatment.[63-69] Successful management of metastases from breast, lung, and colorectal carcinomas have been documented with primary ocular therapy of anti-VEGF injections. Injections are typically given every 1-3 months, depending on tumor response, with regression noted on a follow-up period ranging from 4 to 22 months.[11,70-74]

Conclusion

Choroidal metastasis is the most common intraocular malignancy in the adult population. Choroidal metastases frequently occur in the later stages of disseminated disease and are considered a poor prognostic sign. With increasing treatments available leading to longer survival rates for cancer patients, metastases have the potential to become more prevalent. Effective control of these lesions is imperative. Systemic chemotherapy allows tumor control in some cases, while focal therapy is advised in tumors causing visual loss or is unresponsive to systemic treatment.

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